Special Series

Screening for Cancer
Is It Worth It?

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A delay in diagnosing cancer is widely perceived to compromise severely a patient's chance of being cured. The unrealistic expectations of technology and of physicians' capabilities are inconsistent with modern knowledge of the natural history of cancer. Established and recent precepts in clinical oncology and tumor biology emphasize that inherent characteristics of a malignant neoplasm predict its dissemination, rather than a real or perceived delay in diagnosis. The processes of carcinogenesis and dissemination are more nearly simultaneous than sequential. Uncritical belief in the ability of most cancer screening techniques to provide cure through early detection may do more harm than good. Policy and efforts would be better directed to the primary prevention or reversal of preneoplasia and to improved therapy for established cancer.

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Patients and physicians fear that the failure to diagnose and treat "cancer" immediately will lead to a greater chance of death or disability. This presumes that there is a disease called cancer that has a predictable course, can be detected early if sought, and if found, can be cured by local treatment of the early primary before it spreads. The common reaction to this model is to call for ever-earlier diagnosis and treatment. Modern concepts of cancer care and biology, however, recognize that most patients who die of cancer do so because of inherent characteristics of the cancer, not a physician's inadequacy or a patient's failure to seek and receive care. The biologic characteristics of metastatic cancer provide information not only to guide policy away from broad-based cancer findings and toward prevention or the reversal of preneoplasia, but also to displace the current conventional wisdom and thereby reduce the prevalence of ill-founded litigation.

Physicians and Patients Against Themselves

The medical profession and the laity, perhaps too much influenced by preliminary research, the results of inconclusive clinical trials, and lay-directed news stories, perpetuate the myth of salvation through the early detection of cancer. This puts physicians at increased legal risk and, perhaps more pernicious, lays the blame for their "advanced" disease on the patients themselves, as they may be told by their physician (and their friends): "If only you had been seen earlier." Moreover, with spiraling upward costs, cancer screening is expensive. Standards of care are established by the profession and by the will of society, particularly in the case of screening for preclinical cancer. New technology raises the customary care to a much higher level and creates an environment of unrealistic patient expectations.[1]

The profession recognizes as necessary the continued debate over and the development of screening programs for cancer. If such investigative programs are proselytized as standard of care before efficacy is shown, and survival is not ultimately enhanced, then the result of such inconsistent information is both individual disillusionment with medicine and societal anxiety. The disillusionment and anxiety produce distrust and litigation.

Three Immutable Factors in Cancer Evaluation

In all patients, a precise prognosis and an appropriate therapeutic program for cancer depend on three factors:

- Histologic analysis of the tumor, including type, grade, and, if possible, the characterization of the genetic features of the cancer cells;
- Stage, the apparent extent of the neoplasm at diagnosis; and
- Comorbid conditions that impair treatment and that predict survival in each patient.

The first two factors are tumor characteristics that predict metastasis. Not only do cancers vary in their metastatic potential, but also one primary type of cancer—such as breast or prostate carcinoma—differs among patients in its potential to disseminate. The third factor determines not only whether the cancer will affect survival, but also a patient's ability to survive rigorous

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intervention if that is called for. This three-point appraisal is especially important in the analysis of nonrandomized studies of screening and treatment interventions for cancer. Such studies have been reported to support a no-treatment approach to selected men with prostatic carcinoma.

Those same studies can also be used to show that a delay in diagnosis is often not clinically relevant. The expected survival of the average white man aged 60, 70, and 80 years is about 19, 12, and 17 years, respectively. In a study of 223 men with untreated prostatic carcinoma observed for an average of ten years, more than half died during the decade, but 91% died of something other than their cancer.[2] Moreover, the rate of tumor growth in these men suggested strongly that earlier detection would have made no difference. So, in indolent tumors with low metastatic potential, particularly in hosts with other diseases or old age, early detection makes little difference. Detection may even cause injury if therapy is more traumatic than the natural course of the disease.

At the other end of the spectrum of the natural history of cancer, certain tumors are so virulent that early diagnosis and therapy have no effect. Adenocarcinoma of unknown primary origin is perhaps the most extreme metastatic cancer. A patient is discovered to have widely disseminated cancer without an identifiable primary lesion. There is no opportunity for cure, particularly with modalities of therapy that emphasize regional treatments, such as surgical intervention or irradiation. These unfortunate patients with advanced cancer need strong reassurances that their actions—or lack of earlier action—were not responsible for their metastases.

Cell Kinetics and the Growth of Cancers

A primary 1- to 2-cm neoplasm represents a distinguishable mass of cancer that is the result of a single cell, of a clonal origin, that becomes 1 billion cancer cells admixed with reactive benign cells. This is equivalent to 30 cell doublings; doubling is not determined merely by cell division, but reflects the net proliferative balance between cell division and cell death. Tumor doubling time is used in standard practice to estimate the pace of advancing cancer and is used to make clinical decisions—for example, whether to resect pulmonary metastases that originate from a sarcoma. The doubling time of most tumors of epithelial origin (adenocarcinoma or squamous cell carcinoma) is measured in months, with a biologic life measured in years.

Two studies of carcinoma of the prostate using sequential serum prostate-specific antigen (PSA) measurement provide in vivo corroboration of growth rates of this tumor.[3,4] In the Baltimore Longitudinal Study of Aging, serum specimens were obtained over decades as part of a serum bank in the study cohort of men.[3] The median doubling time computed from serial PSA measurements during the exponential growth phase was three years (range, 1.5 to 6.6 years) for local cancers and two years (0.9 to 8.5 years) for those that were metastatic. A report of 43 patients with diagnosed but untreated carcinoma of the prostate provides confirmatory evidence, as these patients also had a doubling time measured in years.[4] With relatively slow-growing tumors, therefore, it follows that detecting a primary tumor 6 to 12 months or more before standard diagnosis, as is the case in the screening of asymptomatic persons, would merely be detecting in the midpoint of the cancer's life span. Thus "early detection" of many epithelial cancers is a misnomer, and earlier detection may not improve prognosis, but only assure a longer period during which a patient bears the label and anxiety of having known cancer.

If attaining a critical size were mandatory for the metastatic process to be successful, screening for cancer would be a more uniformly successful enterprise. The metastatic cells that result in a person's death emerge long before a clinical diagnosis, however. Achieving a diagnosis 3 to 12 months earlier by screening than by clinical science is often insufficient to alter the death rate from the cancer being studied.

Cancer Biology Provides Clinical Insight

Tumorigenesis—the growth of a primary—is biologically different from the process of metastasis of that same tumor. The most important implication of this biologic reality as regards screening for cancer is that the size of the primary is a relatively unimportant determinant of the metastatic potential of many tumors.

The phenotype recognized as "a malignant neoplasm" is not a single event, but is the manifestation of an accumulation of many alterations in the genotype. These mutations, either inherited or acquired, include the conversion of proto-oncogenes to oncogenes, the loss of tumor suppressor genes, the loss of metastatic suppressor genes, and the inappropriate production or response to growth factors. In fact, critical mutations—most important, those that permit metastasis—may be phenotypically silent during early tumorigenesis. The accumulation of mutations is not sequential, though they are often pictured as such: a tumor may be either local or benign and abruptly, following one more genetic insult, cascade to immediate metastatic disease. The many genetic alterations required for metastasis to evolve are well reviewed.[5]

Discussion

The concept of screening for earlier detection of a cancer implies a monolithic behavior to a type of malignant lesion. In the most general terms, there are three possible behaviors of cancers.[6] One pattern is that of early and rapid evolution of metastases, a situation in which screening will never improve survival and prevention becomes the only possible early intervention. This is exemplified by the many consensus reports that demonstrate no benefit to the use of screening chest radiographs to detect lung cancer. The death rate from cancer is not reduced, as the metastatic cells successfully implant before the threshold of detection is reached.

In a second group of patients, cancers develop with little metastatic potential and should not be sought for in screening programs. The investigations and the natural history of cancer of the prostate support the hypothesis that delayed diagnosis does not necessarily mean harm. In cancer of the prostate, investigators now advocate not only to delay diagnosis, but also to delay instituting therapy for patients with well-differentiated tumors.[7] This represents an acceptance of the fact that a subset of tumors has a lower or absent potential for metastases and that avoiding treatment-related morbidity is of primary import. Patients with these tumors still should be observed clinically to detect any change in the cancer.

This leaves a third group of patients in whom metastases may emerge in a year or two before clinical diagnosis and in whom early detection by screening may make a prognostic difference. For example, regular mammography in women between the ages of 50 and 64 results in a reduction in mortality of about 33%.[8] So far, only cancer of the breast—and in this highly defined subpopulation of women—has been shown to be changed by early detection by screening. The issue of screening for preneoplastic lesions such as leukoplakia, cervical dysplasia, dysplastic nevi, and colonic polyps is entirely separate.

The implication of the data presented here has already affected current case law as regards medical malpractice. If a delay in diagnosis permits metastases to form in distant sites, then the stage is advanced, the prognosis conclusively altered, and litigation is justified under the law. If earlier diagnosis by screening of an already biologically predetermined metastatic cancer does not improve prognosis, then a physician should not be held liable for the failure to diagnose earlier. Two recent California appellate court rulings have upheld the principle that a plaintiff cannot prevail unless it is probable, not simply possible, that a better result would have been obtained in the absence of the perceived negligence.[9,10] Thus a medical malpractice plaintiff may not prevail unless it is determined that the delay in diagnosis and treatment led to the evolution of metastatic cells and was the probable cause of the plaintiff's injury.

Medical, lay, and legal thought have formally accepted that cancers go through a series of steps that include an initial low stage, to a more advanced local stage, to nodal involvement, and finally, to dissemination. Modern thinking discards such a simple, stepwise progression and, rather, considers carcinogenesis and dissemination as processes much more complex. A convincing argument can be constructed on clinical presentation, cell kinetics, and the natural history of the cancer that an interval of a delay in diagnosis rarely alters outcome. Appreciation of these facts may notably alter the prevalence of malpractice litigation in this area.

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